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        117711 ADDITIVE
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                 (LYMPHOMA OR LYMPHOMAS)
L8
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                       PCTFULL COPYRIGHT 2006 Univentio on STN
L8
      ANSWER 1 OF 3
                       1999017799 PCTFULL ED 20020515
ACCESSION NUMBER:
                       CYTOPLASMIC DIPEPTIDYLPEPTIDASE IV FROM HUMAN T-CELLS
TITLE (ENGLISH):
                       DIPEPTIDYLPEPTIDASE IV CYTOPLASMIQUE PROVENANT DE
TITLE (FRENCH):
                       LYMPHOCYTES T D'ORIGINE HUMAINE
INVENTOR(S):
                       BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;
                       HUBER, Brigitte, T.;
                       UNDERWOOD, Robert;
                       KABCENELL, Alisa, K.;
                       SNOW, Roger, J.
PATENT ASSIGNEE(S):
                       TRUSTEES OF TUFTS COLLEGE ET AL.
LANGUAGE OF PUBL.:
                       English
DOCUMENT TYPE:
                       Patent
PATENT INFORMATION:
                                                 DATE
                       NUMBER
                                        KIND
                       ______
                       WO 9917799 A1 19990415
DESIGNATED STATES
                       AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
      W:
                       ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC
                       LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU
                       SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM
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                       CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ
                       CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO .:
                       WO 1998-US20968
                                            A 19981006
                       US 1997-08/944,265
PRIORITY INFO.:
                                               19971006
      ANSWER 2 OF 3
                       PCTFULL COPYRIGHT 2006 Univentio on STN
1.8
                       1999016864 PCTFULL ED 20020515
ACCESSION NUMBER:
                       STIMULATION OF HEMATOPOIETIC CELLS IN VITRO
TITLE (ENGLISH):
TITLE (FRENCH):
                       STIMULATION DE CELLULES HEMATOPOIETIQUES IN VITRO
                       BACHOVCHIN, William;
INVENTOR(S):
                       WALLNER, Barbara
PATENT ASSIGNEE(S):
                       POINT THERAPEUTICS, INC.
LANGUAGE OF PUBL.:
                       English
DOCUMENT TYPE:
                       Patent .
PATENT INFORMATION:
                                        KIND DATE
                       NUMBER
                       WO 9916864
                                          A1 19990408
DESIGNATED STATES
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BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF

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APPLICATION INFO.: WO 1998-US20343 A 19980929 PRIORITY INFO.: US 1997-60/060,306 19970929

L8 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1998024474 PCTFULL ED 20020514
TITLE (ENGLISH): INHIBITION OF INVASIVE REMODELLING
TITLE (FRENCH): INHIBITION DU REMODELAGE INVASIF

INVENTOR(S):
LUND, Leif, Roge;

DANO, Keld; STEPHENS, Ross; BRUENNER, Nils; SOLBERG, Helene; HOLST-HANSEN, Claus; NIELSEN, John, Romer

PATENT ASSIGNEE(S): FONDEN TIL FREMME AF EKSPERIMENTEL CANCERFORSKNING;

LUND, Leif, Roge;

DANO, Keld; STEPHENS, Ross; BRUENNER, Nils; SOLBERG, Helene; HOLST-HANSEN, Claus; NIELSEN, John, Romer

LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent

PATENT INFORMATION:

DESIGNATED STATES

W: AL AM AT AU AZ

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI

CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1997-DK555 A 19971208 PRIORITY INFO.: DK 1996-1402/96 19961206

=> d kwic 1-2

L8 ANSWER 1 OF 3 PCTFULL · COPYRIGHT 2006 Univentio on STN

DETD . . . in therapy in which death of certain cells is therapeutically desirable. For example, in some T-cell neoplastic diseases, e.g.,

leukemias and lymphomas, it may be desirable to de-protect the cancerous \mathbf{T} -

cells from endogenous DPIVb, by inhibiting the enzyme and thus promoting the death. . .

The purified DPlVb of the invention can also be used to make antibodies (polyclonal, monoclonal, or recombinant) using conventional

methods, involving immunization of, e.g., rabbits, mice, or human volunteers.

The antibodies can be used in standard ELISA assays to measure DPIVb levels

in patients being tested for diseases which potentially involve increased. . .

We observed a striking increase in the number of dead cells in cultures containing the L-isomer of Val-boroPro (VbP), an inhibitor of dipeptidyl peptidase IV (DPPIV), compared to cultures containing media alone or the inactive D-isomer of the inhibitor, d-Val-d-boroPro--a toxicity control.

Use as TheraDeutic
Because the punified DPIVb enzyme of the invention is protective of death in normal resting human T-cells, it can be administered therapeutically to patients in need of immune system enhancement, and in particular protection of clinically important T-cell subsets such as CD4' cells. Such patients include
1 5 AIDS patients whose CD4'. . .

Antibodies Directed against DPlVb
The purified DPIVb of the invention, or fragments thereof, can be used
to generate polyclonal or monoclonal antibodies specific for
DPIVb, using
conventional techniques. Such antibodies can be used in any of the many
known conventional immunoassay formats to measure DPIVb levels in biological samples, e.g., samples of. . .

CLMEN 5 An antibody specific for DPIVb.

well were incubated in

L8 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . thymocytes in vitro. Other binding molecules which selectively bind to DPIV and have the ability to stimulate hernatopoietic cells include 'monoclonal antibodies, polyclonal antibodies and fragments of the foregoing which are capable of. (1) binding to DPIV, and (2) stimulating hernatopoietic cells and/or thymocytes in. .

96 microtiter plates in CellGro Iscove's Modified Dulbecco's Medium (IMDM) and with or without (control)'the indicated concentrations of Pro-boroPro for 4 days. At the end of this incubation period, the cells were counted under the microscope. The cultures without ProboroPro contained 10,000 cells at the end of 4 days. The cultures containing Pro-boroPro had 53,000 cells at 10-6M, 38,000 cells at 10-'M and 42,000 cells at 10-'OM. The cultures containing a growth factor mix (GF). Umbilical cord blood cells were incubated under essentially the same conditions as described in the legend to figure 1, except that Val-boroPro was used as stimulant at the indicated concentrations. After 4 day incubation.

A: Bulk Umbilical Cord Blood; Total Cell Counts. Control culture: 0.2 x 106 cells; Growth factors 5 x 106 cells; Val-boroPro: R106 (10-6M); R106 (10-8M); $4 \times 10' (10-'0M)$.

coupled beads

for positive selection. Cell preparation contained 98% CD34+ cells. After 4 days of incubation the culture containing I 0- M Val-boroPro contained 8.5x 106 cells, compared to 0.6xl 06 cells in the control and 4xl 06 cells in the incubation with growth. . .

C: Percent of CD34+ cells remaining after 4 day culture: Cultures incubated with ValboroPro contained between 10 and 15% of CD34+ cells after 4 day culture. Cultures incubated with Growth Factors had only 4% of CD34+ cells remaining (panel b). This indicated that Val-boroPro has a growth stimulatory effect on CD34+ cells in addition to an effect on the differentiation of CD34+ cells into mature peripheral blood cells. This is supported by the observation that culturing these CD34+ cells in the presence of Val-boroPro and growth factors does not change the % CD34+ cells in the culture from the percentage seen with Val-boroPro alone, although the total number of cell in this combined culture had increased to 55 x106 cells as compared to 8.5 x106 cells in the incubation with Val-boroPro

Dimerization of Lys-boroPro (homoconjugate) dramatically increases the stimulation of bone marrow cell growth when compared to the effect of the monomeric form of Lys-boroPro.

Cultures were set up as described in the legend to Figure I except that Lys-boroPro and the homoconjugate were used, and incubated for 4 days.

Figure 4

alone (panel a).

Bone marrow cells were incubated as described in Figure I except that Val-boroPro and the homoconjugate were used in a 4 day culture.

A: Val-boroPro gave a similar expansion of bone marrow cells as the growth factor mix (GF), while the dinier more than doubled the. . .

B: (panel a): Isolated CD34+ cells (98% purity) incubated with ValboroPro gave up to 20 fold increase in stimulation of cellular growth compared to an 18 fold increase with growth factors over that. . .

(panel b): Percent of CD34+ cells remaining in culture after a 4 day incubation period: control 63%; GF 5%; Val-boroPro, 43%; homodinier 10%.

a number of different methods. The most widely used is a positive immunological selection based on binding of these cells to anti-CD34-antibodies immobilized on a solid support (Cellpro, Baxter). Other selection methods include negative selection where all cells not expressing CD34 are isolated away. . .

500 ng/ml. The optimum concentration of each growth factor has to be determined for individual culture conditions

since some growth factors act synergistically with other growth factors. As noted above, the methods of the invention exclude exogenously added cytokines and, instead, utilize DPIV inhibitors to. by observing a reduction in DPIV enzymatic activity following exposure the non-active site binding agent. Exemplary non-active site binding agents include antibodies to DPIV and fragments thereof which selectively bind to DPIV in a manner that results in the ability of the binding. PCT/GB94/02615, DPIV-Serine Protease Inhibitors, Applicant Ferring V.V. (Ferring). Representative examples of the foregoing inhibitors are described below and include the transition-state analog-based inhibitors Xaa-boroPro, include Lys-BoroPro, Pro-BoroPro and Ala-BoroPro in which boroPro refers to the analog of proline in which the carboxylate group (COOH) is replaced with a boronyl group [B(OH)21. Alternative active-site. the ability of the ValboroProline compound to bind to CD26. In a most preferred embodiment, the compound of the invention is Val-boroPro (also referred to as PT-100). Because of the chiral carbon atoms present on the amino acid residues and on the carbon attached to the boron atom, ValboroPro can exist in multiple isomeric forms: (a) L-Val-SboroPro, (b) L-Val-R-boroPro, (c) D-Val-S-boroPro, and (d) D-Val-R-boroPro. More preferably, the compound is L-Val-SboroPro or L-Val-R-boroPro. In an analogous manner, the other boroProline compounds of the invention can exist in multiple isomeric forms; however, in general, the forms in which each amino acid chiral center has an L- configuration and the boroPro is in the R or S configuration are the preferred forms of the compounds. Thus, the invention provides an improved method which synergistically combines hematopoietic cell stimulation with antigen-specific T cell expansion ex vivo. This would be therapeutic for eliciting immune responses against residual tumor cells, metastatic cells, or to enhance the anti-tumor T cell activity in allogeneic transplants. It can also be used for ex vivo expansion of peripheral memory T. skin, breast, cervix, uteri, uterus, ovary, bladder, kidney, brain and other parts of the nervous system, thyroid,

uteri, uterus, ovary, bladder, kidney, brain and other parts of the nervous system, thyroid, prostate, testes, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and leukemia. Viral proteins associated with tumors would be those from the classes of viruses noted above. Antigens characteristic of. . .

Specific examples of tumor antigens include: proteins such as Iq-idiotype of B cell

lymphoma, mutant cyclin-dependent kinase 4 of melanoma, Pmel-1 7 (gp I 00) of melanoma, MART- I (Melan-A) of melanoma, p I. . .

IO, CD26, CD28, CD40, CD44, CD45, B7.1 and B7 According to yet other embodiments, the second targeting moiety is an antibody or antibody fragment that selectively binds to an epitope expressed on the cell surface. The epitope can be a portion of any of the. . .

inhibitor inhibits such DPIV enzymatic activity. Preferably, such binding agents are isolated polypeptides which selectively bind the DPIV. Isolated binding polypeptides include antibodies and fragments of antibodies (e.g. Fab, F(ab)2, Fd and antibody fragments which include a CDR3 region which binds selectively to the DPIV). Preferred isolated binding polypeptides are those that bind to an. . .

The invention, therefore, involves the use of antibodies or fragments of antibodies which have the ability to selectively bind to DPIV and stimulate hematopoietic cells and/or thymocytes under the conditions disclosed herein. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, 1.... Oxford). The pFc'and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFe'region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ablfragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and. . .

The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a $\operatorname{mammalian}$

antibody may be replaced with similar regions of conspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly

manifested in the development and use of humanized antibodies in which non-human

CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional

antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches

the production and use of humanized murine RSV antibodies in which at least a portion of the

murine FR regions have been replaced by FR regions of human origin. Such antibodies,

including fragments of intact antibodies with antigen-binding ability, are often referred to as chimeric antibodies.

to one of ordinary skill in the art, the present invention also provides for F(abl, Fab, Fv and Fd fragments; chimeric antibodies in which the Fe and/or

FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by

homologous human or non-human sequences; chimeric F(ablfragment antibodies in which

the FR and/or CDRI and/or CDR2 and/or light chain CDR3 regions have been replaced by

homologous human or non-human sequences; chimeric Fab fragment antibodies in which the

FR and/or CDRI and/or CDR2 and/or light chain CDR3 regions have been replaced by

homologous human or non-human sequences; and chimeric Fd fragment antibodies in which

the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non- $\,$

human sequences. The present invention also includes so-called single chain antibodies.

and type that bind specifically to

DPIV and inhibit its functional activity. These polypeptides may be derived also from $% \left(1\right) =\left(1\right) +\left(1$

sources other than antibody technology. For example, such polypeptide binding agents can

be provided by degenerate peptide libraries which can be readily prepared in solution,. . .

the matrix permits covalent coupling to free amino groups. A polystyrene derivatized to carry carboxylate groups can be covalently attached

directly to Lys-boroPro through coupling to the free E amino group of the Lys side chain, or

through a spacer linker which has a free amino group. Alternatively, a polystyrene

derivatized to carry an amino group can be attached to, for example, Lys-boroPro through

coupling via a spacer linker containing two carboxylate groups, one to couple to the F amino

group of Lys-boroPro, the other to the amino group of the amino-derivatized polystyrene.

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the
       attachment of the compounds of the invention to insoluble matrices.
       Biotin can easily be
       attached to the E amino group of Lys-boroPro for example and
       the resulting conjugate will
       adhere with high affinity to avidin or strepavidin. A wide assortment of
       insolubilized
       derivatives of.
       well or 24 well microtiter
       plates) at 104 cells/ml in CellGro Iscove's Modified Dulbecco's medium
       (Meditech)
       containing kanamycin (5ug/ml), desired concentration of Xaa-
       boroPro or other
       compound of the invention, and the absence or presence of Giant Cell
       Tumor-
       Conditioned Medium (GCT-CM, Origen) as source of growth factors. Xaa-
       boroPro or
       other compounds of the invention should be diluted to medium and added
       to culture only
       after cells are in culture tube.
CLMEN 5 The method of claim 1, wherein the inhibitor of DPIV is selected from
       the group
       consisting of a Lys-boroPro monomer, a Pro-boroPro
       monomer, a Val-boroPro monomer and a
       Lys-boroPro conjugate.
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     FILE 'DGENE' ENTERED AT 08:18:01 ON 29 JUN 2006
     FILE 'PCTFULL' ENTERED AT 08:18:10 ON 29 JUN 2006
             39 S BOROPRO OR PROBORO OR VALBOROPRO
             24 S ANTIBOD? AND L1
         357416 S ADDITIVE OR SYNERG? OR ENHANC?
             22 S L3 AND L2
             12 S L4 NOT PY>2001
             10 S L4 NOT PY>2000
              0 S L6 AND CD20
              3 S L6 AND LYMPHOMA
=> s 14 and CD20
        · 2487 CD20
             2 L4 AND CD20
=> d ibib 1-2
                                   COPYRIGHT 2006 Univentio on STN
       ANSWER 1 OF 2
                        PCTFULL
ACCESSION NUMBER:
                        2004004661 PCTFULL ED 20040122 EW 200403
                        BOROPROLINE COMPOUND COMBINATION THERAPY
TITLE (ENGLISH):
                        POLYTHERAPIE A BASE DE COMPOSES DE BOROPROLINE
TITLE (FRENCH):
INVENTOR(S):
                        ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451,
                        MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA
                        01860, US;
                        JESSON, Michael, I., 19 Plain Street, Hopedale, MA
                        01747, US;
                        JONES, Barry, 80 Wndell, No.3, Cambridge, MA 02138, US
                        POINT THERAPEUTICS, INC., 125 Summer Street, Suite
PATENT ASSIGNEE(S):
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1840, Boston, MA 02111, US [US, US]

L1L2

L3

L4

L5

L6

L7

·L8

L9

L9

AGENT: TREVISAN, Maria, A.\$, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210\$, US LANGUAGE OF FILING: English LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND DATE -----WO 2004004661 A2 20040115 DESIGNATED STATES W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW RW (EAPO): AM AZ BY KG KZ MD RU TJ TM AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU RW (EPO): MC NL PT RO SE SI SK TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG RW (OAPI): WO 2003-US21547 A 20030709 APPLICATION INFO.: PRIORITY INFO.: US 2002-60/394,856 20020709 US 2002-60/414,978 20021001 US 2003-60/466,435 20030428 L9 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN ACCESSION NUMBER: 2004004658 PCTFULL ED 20040122 EW 200403 TITLE (ENGLISH): METHODS AND COMPOSITIONS RELATING TO ISOLEUCINE BOROPROLINE COMPOUNDS TITLE (FRENCH): PROCEDES ET COMPOSITIONS AYANT TRAIT A DES COMPOSES D'ISOLEUCINE BOROPROLINE ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451, INVENTOR(S): US; MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA 01860, US; JESSON, Michael, I., 19 Plain Street, Hopedale, MA 01747, US; JONES, Barry, 80 Wendell Street, #3, Cambridge, MA 02138, US POINT THERAPEUTICS, INC., 125 Summer Street, Suite PATENT ASSIGNEE(S): 1840, Boston, MA 02111, US [US, US] TREVISAN, Maria, A.\$, Wolf, Greenfield & Sacks, P.C., AGENT: 600 Atlantic Avenue, Boston, MA 02210\$, US LANGUAGE OF FILING: English English LANGUAGE OF PUBL.: DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND DATE ______ WO 2004004658 A2 20040115 DESIGNATED STATES W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW RW (ARIPO): RW (EAPO): AM AZ BY KG KZ MD RU TJ TM AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU RW (EPO): MC NL PT RO SE SI SK TR RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG APPLICATION INFO.: WO 2003-US21405 A 20030709 PRIORITY INFO.: US 2002-60/394,856 20020709

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US 2002-60/414,978 20021001
US 2003-60/466,435 20030428
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=> s anti () CD20 177657 ANTI 177 ANTIS 177694 ANTI (ANTI OR ANTIS) 2487 CD20 L10 1049 ANTI (W) CD20 => d·his (FILE 'HOME' ENTERED AT 08:17:16 ON 29 JUN 2006) FILE 'DGENE' ENTERED AT 08:18:01 ON 29 JUN 2006 FILE 'PCTFULL' ENTERED AT 08:18:10 ON 29 JUN 2006 L139 S BOROPRO OR PROBORO OR VALBOROPRO L224 S ANTIBOD? AND L1 L3357416 S ADDITIVE OR SYNERG? OR ENHANC? L422 S L3 AND L2 L5 .12 S L4 NOT PY>2001 $_{\rm L6}$ 10 S L4 NOT PY>2000 L7 0 S L6 AND CD20 L8 3 S L6 AND LYMPHOMA L9 2 S L4 AND CD20 1049 S ANTI () CD20 T.10 => s 110 and 14 2 L10 AND L4 L11=> d ibib 1-2 L11 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN ACCESSION NUMBER: 2004004661 PCTFULL ED 20040122 EW 200403 TITLE (ENGLISH): BOROPROLINE COMPOUND COMBINATION THERAPY TITLE (FRENCH): POLYTHERAPIE A BASE DE COMPOSES DE BOROPROLINE INVENTOR(S): ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451, MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA 01860, US; JESSON, Michael, I., 19 Plain Street, Hopedale, MA 01747, US; JONES, Barry, 80 Wndell, No.3, Cambridge, MA 02138, US PATENT ASSIGNEE(S): POINT THERAPEUTICS, INC., 125 Summer Street, Suite 1840, Boston, MA 02111, US [US, US] AGENT: TREVISAN, Maria, A.\$, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210\$, US LANGUAGE OF FILING: English LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND -----WO 2004004661 A2 20040115 DESIGNATED STATES W : .AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA

GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

ZM ZW

RW (ARIPO):

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU RW (EPO): MC NL PT RO SE SI SK TR BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG RW (OAPI): APPLICATION INFO.: WO 2003-US21547 A 20030709 PRIORITY INFO.: US 2002-60/394,856 20020709 US 2002-60/414,978 20021001 US 2003-60/466,435 20030428 ANSWER 2 OF 2 COPYRIGHT 2006 Univentio on STN L11PCTFULL ACCESSION NUMBER: 2004004658 PCTFULL ED 20040122 EW 200403 TITLE (ENGLISH): METHODS AND COMPOSITIONS RELATING TO ISOLEUCINE BOROPROLINE COMPOUNDS TITLE (FRENCH): PROCEDES ET COMPOSITIONS AYANT TRAIT A DES COMPOSES D'ISOLEUCINE BOROPROLINE INVENTOR(S): ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451, MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA 01860, US; JESSON, Michael, I., 19 Plain Street, Hopedale, MA 01747, US; JONES, Barry, 80 Wendell Street, #3, Cambridge, MA 02138, US PATENT ASSIGNEE(S): POINT THERAPEUTICS, INC., 125 Summer Street, Suite 1840, Boston, MA 02111, US [US, US] AGENT: TREVISAN, Maria, A.\$, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210\$, US LANGUAGE OF FILING: English LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND DATE ______ WO 2004004658 A2 20040115 DESIGNATED STATES W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC'LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZW RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW RW (EAPO): AM AZ BY KG KZ MD RU TJ TM RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR RW (OAPI): BF BJ CF CG CI CM GA GN GO GW ML MR NE SN TD TG APPLICATION INFO.: WO 2003-US21405 A 20030709 US 2002-60/394,856 PRIORITY INFO.: 20020709 US 2002-60/414,978 20021001 US 2003-60/466,435 20030428

=> s boroproline

L12 28 BOROPROLINE

=> s 112 and 110

L13 2 L12 AND L10

=> d ibib 1-2

L13 ANSWER 1 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN ACCESSION NUMBER: 2004004661 PCTFULL ED 20040122 EW 200403 TITLE (ENGLISH): BOROPROLINE COMPOUND COMBINATION THERAPY TITLE (FRENCH): POLYTHERAPIE A BASE DE COMPOSES DE BOROPROLINE

INVENTOR(S): ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451,

```
MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA
                        01860, US;
                        JESSON, Michael, I., 19 Plain Street, Hopedale, MA
                        01747, US;
                        JONES, Barry, 80 Wndell, No.3, Cambridge, MA 02138, US
PATENT ASSIGNEE(S):
                        POINT THERAPEUTICS, INC., 125 Summer Street, Suite
                        1840, Boston, MA 02111, US [US, US]
AGENT:
                        TREVISAN, Maria, A.$, Wolf, Greenfield & Sacks, P.C.,
                        600 Atlantic Avenue, Boston, MA 02210$, US
LANGUAGE OF FILING:
                        English
LANGUAGE OF PUBL.:
                        English
DOCUMENT TYPE:
                        Patent
PATENT INFORMATION:
                       NUMBER
                                          KIND
                                                   DATE
                        ______
                       WO 2004004661
                                           A2 20040115
DESIGNATED STATES
                       AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
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                       CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                       IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
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                       ZM ZW
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                       GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
      RW (EAPO):
                       AM AZ BY KG KZ MD RU TJ TM
      RW (EPO):
                       AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                       MC NL PT RO SE SI SK TR
      RW (OAPI):
                       BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:
                       WO 2003-US21547
                                            A 20030709
PRIORITY INFO.:
                       US 2002-60/394,856
                                               20020709
                       US 2002-60/414,978
                                               20021001
                       US 2003-60/466,435
                                               20030428
L13
      ANSWER 2 OF 2
                        PCTFULL
                                  COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:
                       2004004658 PCTFULL ED 20040122 EW 200403
TITLE (ENGLISH):
                       METHODS AND COMPOSITIONS RELATING TO ISOLEUCINE
                       BOROPROLINE COMPOUNDS
TITLE (FRENCH):
                       PROCEDES ET COMPOSITIONS AYANT TRAIT A DES COMPOSES
                       D'ISOLEUCINE BOROPROLINE
INVENTOR(S):
                       ADAMS, Sharlene, 45 Rosemont Avenue, Waltham, MA 02451,
                       MILLER, Glenn, T., 63 Bearhill Road, Merrimac, MA
                       01860, US;
                       JESSON, Michael, I., 19 Plain Street, Hopedale, MA
                       01747, US;
                       JONES, Barry, 80 Wendell Street, #3, Cambridge, MA
                       02138, US
PATENT ASSIGNEE(S):
                       POINT THERAPEUTICS, INC., 125 Summer Street, Suite
                       1840, Boston, MA 02111, US [US, US]
AGENT:
                       TREVISAN, Maria, A.$, Wolf, Greenfield & Sacks, P.C.,
                       600 Atlantic Avenue, Boston, MA 02210$, US
LANGUAGE OF FILING:
                       English
LANGUAGE OF PUBL.:
                       English
DOCUMENT TYPE:
                       Patent
PATENT INFORMATION:
                       NUMBER
                                         KIND
                                                   DATE
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                       WO 2004004658
                                           A2 20040115
DESIGNATED STATES
      W:
                       AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                       CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                       IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
                       MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD
                       SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA
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       RW (EAPO):
                        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):
                        AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                        MC NL PT RO SE SI SK TR
       RW (OAPI):
                        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:
                        WO 2003-US21405
                                              A 20030709
PRIORITY INFO.:
                        US 2002-60/394,856
                                                 20020709
                        US 2002-60/414,978
                                                 20021001
                        US 2003-60/466,435
                                                 20030428
=> s B () cell
        680860 B
        222708 CELL
        192476 CELLS
        252846 CELL
                  (CELL OR CELLS)
L14
         25810 B (W) CELL
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     (FILE 'HOME' ENTERED AT 08:17:16 ON 29 JUN 2006)
   FILE 'DGENE' ENTERED AT 08:18:01 ON 29 JUN 2006
     FILE 'PCTFULL' ENTERED AT 08:18:10 ON 29 JUN 2006
L1
             39 S BOROPRO OR PROBORO OR VALBOROPRO
L2
             24 S ANTIBOD? AND L1
L3
         357416 S ADDITIVE OR SYNERG? OR ENHANC?
            22 S L3 AND L2
L4
L5
             12 S L4 NOT PY>2001
L6
             10 S L4 NOT PY>2000
L7
              0 S L6 AND CD20
rs
              3 S L6 AND LYMPHOMA
L9
              2 S L4 AND CD20
L10
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L11
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L12
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L13
              2 S L12 AND L10
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L14
=> s 114 and 12
L15
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\Rightarrow s 12 and CD20
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             2 L2 AND CD20
L16
=> s 115 not py>2001
        518014 PY>2001
L17
             6 L15 NOT PY>2001
=> d ibib 1-6
L17
       ANSWER 1 OF 6
                         PCTFULL COPYRIGHT 2006 Univentio on STN
                        2001016301 PCTFULL ED 20020828
ACCESSION NUMBER:
                        QUIESCENT CELL DIPEPTIDYL PEPTIDASE: A NOVEL
TITLE (ENGLISH):
                        CYTOPLASMIC SERINE PROTEASE
                        DIPEPTIDYL PEPTIDASE DE CELLULE QUIESCENTE: UNE
TITLE (FRENCH):
                        NOUVELLE SERINE PROTEASE CYTOPLASMIQUE
                        HUBER, Brigitte, T.;
INVENTOR(S):
                        UNDERWOOD, Robert, H.
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TUFTS UNIVERSITY;

HUBER, Brigitte, T.;

PATENT ASSIGNEE(S):

UNDERWOOD, Robert, H.

DOCUMENT TYPE: Patent

PATENT INFORMATION: .

DESIGNATED STATES

. W:

AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC

NL PT SE

APPLICATION INFO.: WO 2000-US24052 A 20000901 PRIORITY INFO.: US 1999-09/388,413 19990901

L17 ANSWER 2 OF 6

ACCESSION NUMBER: TITLE (ENGLISH): TITLE (FRENCH):

PCTFULL COPYRIGHT 2006 Univentio on STN

1999017799 PCTFULL ED 20020515

CYTOPLASMIC DIPEPTIDYLPEPTIDASE IV FROM HUMAN T-CELLS DIPEPTIDYLPEPTIDASE IV CYTOPLASMIQUE PROVENANT DE

LYMPHOCYTES T D'ORIGINE HUMAINE

INVENTOR(S): BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.;

HUBER, Brigitte, T.;
UNDERWOOD, Robert;
KABCENELL, Alisa, K.;

SNOW, Roger, J.

PATENT ASSIGNEE(S): LANGUAGE OF PUBL.: TRUSTEES OF TUFTS COLLEGE ET AL.

English Patent

DOCUMENT TYPE:

PATENT INFORMATION:

NUMBER KIND DATE
----WO 9917799 A1 19990415

DESIGNATED STATES

₩:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ

 $\mbox{CF CG CI CM GA GN GW ML MR NE SN TD TG}$

PCTFULL COPYRIGHT 2006 Univentio on STN

STIMULATION OF HEMATOPOIETIC CELLS IN VITRO

APPLICATION INFO.: PRIORITY INFO.:

WO 1998-US20968 A 19981006 US 1997-08/944,265 19971006

1999016864 PCTFULL ED 20020515

L17 ANSWER 3 OF 6
ACCESSION NUMBER:
TITLE (ENGLISH):
TITLE (FRENCH):

STIMULATION DE CELLULES HEMATOPOIETIQUES IN VITRO BACHOVCHIN, William; WALLNER, Barbara

PATENT ASSIGNEE(S): LANGUAGE OF PUBL.:

INVENTOR(S):

DOCUMENT TYPE:
PATENT INFORMATION:

POINT THERAPEUTICS, INC.

English Patent

DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF

APPLICATION INFO.: PRIORITY INFO.:

WO 1998-US20343 A 19980929 US 1997-60/060,306 19970929

BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

L17 ANSWER 4 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN

1998050066 PCTFULL ED 20020514 ACCESSION NUMBER: TITLE (ENGLISH): POTENTIATION OF THE IMMUNE RESPONSE THROUGH DELIVERY OF COMPOUNDS BINDING A CYTOPLASMIC DIPEPTIDASE TITLE (FRENCH): POTENTIALISATION DE LA REPONSE IMMUNITAIRE PAR

PRODUCTION DE COMPOSES SE FIXANT A UNE DIPEPTIDASE

CYTOPLASMIQUE

HUBER, Brigitte, T.; INVENTOR(S): SCHMITZ, Tracy;

UNDERWOOD, Robert

TRUSTEES OF TUFTS COLLEGE PATENT ASSIGNEE(S):

LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER KIND DATE _____ WO 9850066 A1 19981112

DESIGNATED STATES

AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC W:

NL PT SE

WO 1998-US8838 APPLICATION INFO.: A 19980430 US 1997-8/852,395 PRIORITY INFO.: 19970507

ANSWER 5 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN L17

ACCESSION NUMBER: 1998024474 PCTFULL ED 20020514 TITLE (ENGLISH): INHIBITION OF INVASIVE REMODELLING INHIBITION DU REMODELAGE INVASIF TITLE (FRENCH): INVENTOR(S): LUND, Leif, Roge;

DANO, Keld; STEPHENS, Ross; BRueNNER, Nils; SOLBERG, Helene; HOLST-HANSEN, Claus; NIELSEN, John, Romer

FONDEN TIL FREMME AF EKSPERIMENTEL CANCERFORSKNING; PATENT ASSIGNEE(S):

LUND, Leif, Roge;

DANO, Keld; STEPHENS, Ross; BRueNNER, Nils; SOLBERG, Helene; HOLST-HANSEN, Claus; NIELSEN, John, Romer

LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION:

NUMBER KIND DATE -----WO 9824474 A1 19980611

DESIGNATED STATES

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE W: ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR

LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI

CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1997-DK555 A 19971208 DK 1996-1402/96 PRIORITY INFO.: 19961206

ANSWER 6 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN T.17

ACCESSION NUMBER: 1998000439 PCTFULL ED 20020514

MULTIVALENT COMPOUNDS FOR CROSS-LINKING RECEPTORS AND TITLE (ENGLISH):

USES THEREOF

COMPOSES MULTIVALENTS POUR LA RETICULATION DE TITLE (FRENCH):

RECEPTEURS ET UTILISATIONS ASSOCIES

INVENTOR(S): BACHOVCHIN, William, W. PATENT ASSIGNEE(S): TRUSTEES OF TUFTS COLLEGE;

BACHOVCHIN, William, W.

LANGUAGE OF PUBL.: DOCUMENT TYPE:

English Patent

PATENT INFORMATION:

NUMBER KIND DATE WO 9800439 A2 19980108

DESIGNATED STATES

W:

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR

NE SN TD TG

APPLICATION INFO.: PRIORITY INFO.:

WO 1997-US11279 A 19970627 US 1996-8/671,756 19960628 US 1997-8/837,305 19970411

=> d kwic 2-5

L17 ANSWER 2 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD The purified DP1Vb of the invention can also be used to make antibodies (polyclonal, monoclonal, or recombinant) using conventional

methods, involving immunization of, e.g., rabbits, mice, or human volunteers.

The antibodies can be used in standard ELISA assays to measure $\ensuremath{\mathsf{DPIVb}}$ levels

in patients being tested for diseases which potentially involve increased. . .

We observed a striking increase in the number of dead cells in cultures containing the L-isomer of Val-boroPro (VbP), an inhibitor of

dipeptidyl peptidase IV (DPPIV), compared to cultures containing media alone

or the inactive D-isomer of the inhibitor, d-Val-d-boroPro--a toxicity control.

Dead cells were apparent as early as 4 h after the addition of the L-isomer of

VbP, with maximal death occurring. . . 24 h (about 70%). When subpopulations of PBMC were tested for susceptibility to VbP- induced death,

we observed that CD 1 9' B cells and CD I I b' monocytes were resistant, while

purified T-cells (CD4'/CD8') showed greater sensitivity than whole PBMC.

(44-blotin, Sigma), and

phycoerythrin streptavidin, CD26' T cells were isolated by sorting with the

anti-CD26 mAb 1F7 (C. Moninioto, Dana-Farber Cancer Inst.). B cells were

isolated by selection with blotinyl-anti-CD 1 9 rnAb (D. Thorley Lawson, Tufts $\dot{}$

Univ.) And MACS microbeads (Miltenyl Blotec'). Sorted cell populations.

Antibodies Directed against DPlVb
The purified DPIVb of the invention, or fragments thereof, can be

used to generate polyclonal or monoclonal antibodies specific for DPIVb, using conventional techniques. Such antibodies can be used in any of known conventional immunoassay formats to measure DPIVb levels in biological samples, e.g., samples of. CLMEN 5 An antibody specific for DPIVb. ANSWER 3 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN . ability to proliferate and exhibit morphological characteristics specific for their lineages (such as macrophages, granulocytes, platelets, red blood cells, T cells and B cells). Stem cells and progenitor cells express CD34 on their surface while differentiated cells do not. Bone marrow includes stem cells as well as progenitor cells of the lymphoid (T and B cells), myeloid (granulocytes, macrophages) and erythroid (red blood cells) lineages. thymocytes in vitro. Other binding molecules which selectively bind to DPIV and have the ability to stimulate hernatopoietic cells include monoclonal antibodies, polyclonal antibodies and fragments of the foregoing which are capable of. (1) binding to DPIV, and (2) stimulating hernatopoietic cells and/or thymocytes in. well were incubated in 96 microtiter plates in CellGro Iscove's Modified Dulbecco's Medium (IMDM) and with or without (control)'the indicated concentrations of Pro-boroPro for 4 days. At the end of this incubation period, the cells were counted under the microscope. The cultures without ProboroPro contained 10,000 cells at the end of 4 days. The cultures containing Pro-boroPro had 53,000 cells at 10-6M, 38,000 cells at 10-'M and 42,000 cells at 10-'OM. The cultures containing a growth factor mix (GF). . Umbilical cord blood cells were incubated under essentially the same conditions as described in the legend to figure 1, except that Val-boroPro was used as stimulant at the indicated concentrations. After 4 day incubation. A: Bulk Umbilical Cord Blood; Total Cell Counts. Control culture: 0.2 x 106 cells; Growth factors 5 x 106 cells; Val-boroPro: R106 (10-6M); R106 (10-8M); $4\times10'(10-'OM)$. coupled beads for positive selection. Cell preparation contained 98% CD34+ cells. After 4 days of incubation the culture containing I 0- M Val-boroPro contained 8.5x 106 cells, compared to 0.6xl 06 cells in the control and 4xl 06 cells in the incubation with growth.

C: Percent of CD34+ cells remaining after 4 day culture: Cultures

boroPro contained between 10 and 15% of CD34+ cells after 4

incubated with Val-

L17

DETD

day culture. Cultures incubated with Growth Factors had only 4% of CD34+ cells remaining (panel b). This indicated that .Val-boroPro has a growth stimulatory effect on CD34+ cells in addition to an effect on the differentiation of CD34+ cells into mature peripheral blood cells. This is supported by the observation that culturing these CD34+ cells in the presence of Val-boroPro and growth factors does not change the % CD34+ cells in the culture from the percentage seen with Val-boroPro alone, although the total number of cell in this combined culture had increased to 55 x106 cells as compared to 8.5 x106 cells in the incubation with Val-boroPro alone (panel a).

Dimerization of Lys-boroPro (homoconjugate) dramatically increases the stimulation of bone marrow cell growth when compared to the effect of the monomeric form of Lys-boroPro.

Cultures were set up as described in the legend to Figure I except that Lys-boroPro and the homoconjugate were used, and incubated for 4 days.

Figure 4

Bone marrow cells were incubated as described in Figure I except that Val-boroPro and the homoconjugate were used in a 4 day culture.

A: Val-boroPro gave a similar expansion of bone marrow cells as the growth factor mix (GF), while the dinier more than doubled the. . .

B: (panel a): Isolated CD34+ cells (98% purity) incubated with ValboroPro gave up to 20 fold increase in stimulation of cellular growth compared to an 18 fold increase with growth factors over that. . . .

(panel b): Percent of CD34+ cells remaining in culture after a 4 day incubation period: control 63%; GF 5%; Val-boroPro, 43%; homodinier 10%.

ability to proliferate and exhibit morphological characteristics specific for their lineages (such as macrophages, granulocytes, platelets, red blood cells, T cells and B cells). Bone marrow includes stem cells as well as progenitor cells of the lymphoid (T and B cells), inyeloid (e.g., granulocytes, macrophages) and erythroid (red blood cells) lineages. Stem cells and progenitor cells express CD34 on their surface while differentiated. . .

a number of different methods. The most widely used is a positive immunological selection based on binding of these cells to anti-CD34-antibodies immobilized on a solid support (Cellpro, Baxter). Other selection methods include negative selection where all cells not expressing CD34 are isolated away. . .

by observing a reduction in DPIV enzymatic activity following exposure to

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the non-active site binding agent. Exemplary non-active site binding
agents include
  antibodies to DPIV and fragments thereof which selectively
bind to DPIV in a manner that
results in the ability of the binding.
PCT/GB94/02615, DPIV-Serine
Protease Inhibitors, Applicant Ferring V.V. (Ferring). Representative
examples of the
foregoing inhibitors are described below and include the
transition-state analog-based
inhibitors Xaa-boroPro, include Lys-BoroPro, Pro-
BoroPro and Ala-BoroPro in which
  boroPro refers to the analog of proline in which the
carboxylate group (COOH) is replaced
with a boronyl group [B(OH)21. Alternative active-site.
the ability of the Val-
boroProline compound to bind to CD26. In a most preferred embodiment,
the compound of
the invention is Val-boroPro (also referred to as PT-100).
Because of the chiral carbon
atoms present on the amino acid residues and on the carbon attached to
the boron atom, Val-
  boroPro can exist in multiple isomeric forms: (a) L-Val-S-
boroPro, (b) L-Val-R-boroPro, (c)
D-Val-S-boroPro, and (d) D-Val-R-boroPro. More
preferably, the compound is L-Val-S-
  boroPro or L-Val-R-boroPro. In an analogous manner,
the other boroProline compounds of
the invention can exist in multiple isomeric forms; however, in general,
the forms in which
each amino acid chiral center has an L- configuration and the
boroPro is in the R or S
configuration are the preferred forms of the compounds.
The preferred antigenic peptides are peptides that bind to a T cell
surface receptor or a B cell
surface receptor, e.g., TCR/CD3, CD2, CD4, CD8, CD IO, CD26, CD28, CD40,
CD45, B7.1
and B7
Alternatively, the reactive moiety can be.
major histocompatibility complex
(MHC) molecule) which is present on the surface of a T cell or on the
surface of a B cell. In
certain embodiments, the second targeting moiety has a structure which
mimics the substrate
binding site of a protease that is present.
Specific examples of tumor antigens include: proteins such as
Ig-idiotype of B cell
lymphoma, mutant cyclin-dependent kinase 4 of melanoma, Pmel- 1 7 (gp I
00) of melanoma,
MART- I (Melan-A) of melanoma, p I. . .
that selectively
binds to a receptor that is expressed on the surface of a cell
(preferably a T cell or a B cell).
IO, CD26, CD28, CD40, CD44, CD45, B7.1 and B7
According to yet other embodiments, the second targeting moiety is an
antibody or antibody
fragment that selectively binds to an epitope expressed on the cell
surface. The epitope can
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be a portion of any of the. .

inhibitor inhibits such DPIV enzymatic activity. Preferably, such binding agents are isolated polypeptides which selectively bind the DPIV. Isolated binding polypeptides include antibodies and fragments of antibodies (e.g. Fab, F(ab)2, Fd and antibody fragments which include a CDR3 region which binds selectively to the DPIV). Preferred isolated binding polypeptides are those that bind to an. . .

The invention, therefore, involves the use of antibodies or fragments of antibodies which have the ability to selectively bind to DPIV and stimulate hematopoietic cells and/or thymocytes under the conditions disclosed herein. Antibodies include polyclonal and monoclonal antibodies, prepared according to conventional methodology.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W.R. (1986) The Experimental Foundations of Modern Immunology Wiley & Sons, Inc., New York; Roitt, 1... Oxford). The pFc'and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFe'region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ablfragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and. . .

The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of conspecific or heterospecific antibodies

while retaining the epitopic specificity of the original

antibody. This is most clearly manifested in the development and use of humanized antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. Thus, for example, PCT International Publication Number WO 92/04381 teaches the production and use of humanized murine RSV antibodies in which at least a portion of the murine FR regions have been replaced by FR regions of human origin. Such antibodies, including fragments of intact antibodies with antigen-binding ability, are often referred to as chimeric antibodies. to one of ordinary skill in the art, the present invention also provides for F(abl, Fab, Fv and Fd fragments; chimeric antibodies in which the Fe and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric F(ablfragment antibodies in which the FR and/or CDRI and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the .FR and/or CDRI and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or nonhuman sequences. The present invention also includes so-called single chain antibodies. and type that bind specifically to DPIV and inhibit its functional activity. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide libraries which can be readily prepared in solution,. the matrix permits covalent coupling to free amino groups. A polystyrene derivatized to carry carboxylate groups can be covalently attached directly to Lys-boroPro through coupling to the free E amino group of the Lys side chain, or through a spacer linker which has a free amino group. Alternatively, a polystyrene derivatized to carry an amino group can be attached to, for example, Lys-boroPro through coupling via a spacer linker containing two carboxylate groups, one to couple to the F amino group of Lys-boroPro, the other to the amino group of the amino-derivatized polystyrene. the attachment of the compounds of the invention to insoluble matrices. Biotin can easily be attached to the E amino group of Lys-boroPro for example and the resulting conjugate will adhere with high affinity to avidin or strepavidin. A wide assortment of insolubilized derivatives of.

```
well or 24 well microtiter
       plates) at 104 cells/ml in CellGro Iscove's Modified Dulbecco's medium
       (Meditech)
       containing kanamycin (5ug/ml), desired concentration of Xaa-
       boroPro or other
       compound of the invention, and the absence or presence of Giant Cell
       Tumor-
       Conditioned Medium (GCT-CM, Origen) as source of growth factors. Xaa-
       boroPro or
       other compounds of the invention should be diluted to medium and added
       to culture only
       after cells are in culture tube.
CLMEN 5 The method of claim 1, wherein the inhibitor of DPIV is selected from
       the group
       consisting of a Lys-boroPro monomer, a Pro-boroPro
       monomer, a Val-boroPro monomer and a
       Lys-boroPro conjugate.
      ANSWER 4 OF 6
                         PCTFULL
                                   COPYRIGHT 2006 Univentio on STN
DETD
      . . . T-cell stimulatory effects of two inhibitory compounds
       used according to the invention (date of experiment: 3/9/95; patient id
       no: 1 655185; CD4
         antibody count: 760; and number of cells/well: 0.4 x 106).
       invention
       in lymphocytes of HIV-infected patients, compared to treatment using two
       control compounds
       (date of experiment: 3/15/95; patient id no: 1227604; CD4
       antibody count: 230; number of
       cells/well: 0. 16 x IO'; and 1/2area of a 96 well plate).

    invention

       in lymphocytes of HIV-infected patients, compared to treatment using two
       control compounds
       (date of experiment 3/23/95; patient id no. 1586496; CD4
       antibody count: 830; number of
       6)
       cells/well: 0.4 \times 10
       Fig. 5 is a graph illustrating a stimulatory effect of an inhibitor
       according to.
       invention induces
       dose-dependent apoptosis in resting T-cells (these dosages are higher
       than the extremely low
       doses used according to the invention). CD 19+B cells
       and CD4+/CD8+Tcells were isolated
       (>90% and >97% purity, respectively). The cells were then incubated
       overnight in the presence
       or absence of VBBP.
      CD26 PBMC populations were found to be equally
       susceptible to DPPIV inhibitor induced death. PBMC were stained with the
       anti-CD26
       io monoclonal antibody, 4 EL, and then sorted into CD26+ and
       CD26- populations using a facstar
       plus dual lasar flow cytometry. The cells expressing. . . isolated as
       the CD26+ and CD26
       populations respectively. The purity of the populations as examined by
       staining with the anti-
      CD26 monoclonal antibody, 134-2C2, is >90%. The CD26+ and
      CD26_ populations were
       cultured overnight in the presence or absence of various concentrations
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L17

of VBP.. .

Fig. 8 is a graph showing that an inhibitor of CD26 (val-boroPro) inhibited the cytoplasmic enzyme as well.

hereby incorporated by reference. In this application, one of the families of molecules in the '493 patent is described as the XaaboroPro molecules,

exemplified by Ala-boroPro, Pro-boroPro, and Gly-

boroPro. These Xaa-boroPro molecules are

all candidate compounds for use in the methods of the present invention. Two of these

compounds are used in some of the examples described below; those compounds are Lys-

boroPro (KPB) and Val-boroPro (VBP).

very low doses of the Val-boroPro and Lys-boroPro stimulated proliferation of PBMC from HIV-infected patients, but not PBMC from uninfected patients.

As shown in Fig. 1, at no concentration of the boroPro enzyme inhibitor did it affect the PBMC from uninfected individuals. The inhibitor, at moderate concentrations, also did not cause proliferation of PBMC. . .

Concordant results are shown in Fig. 2, a histogram showing that low doses of Lys-

boroPro and Val-boroPro cause proliferation of PBMC of HIV-infected patients, while higher doses (I O-'M) do not have this effect.

Fig. 6 is a graph demonstrating that purified T-cells are highly sensitive to cytoplasmic T-cell dipeptidase inhibitors in moderate concentrations. CD19'B cells and CD4'/CD8' T-cells

were isolated to high purity and incubated overnight in Val-

boroPro. The amount of cell death
was determined by 7AAD flow cytometry analysis. Data represent

was determined by 7AAD flow cytometry analysis. Data represent % of cell death from

duplicate samples. These. .

the inhibitor is

administered immoderate concentrations. CD26' and CD26- populations were incubated

overnight in the presence or absence of various concentrations of ValboroPro. The amount of

cell death was determined by 7AAD flow cytometry analysis. Data represent mean % of death from duplicate samples. These. . .

Fig. 8 presents data showing the effects of an inhibitor useful in the invention, Val-

boroPro. The experiments were carried out using two preparations: purified DPPIV (i.e.,

CD26), and Jurkat T-cell cytoplasmic extract, described above (Jurkat cells contain the

cytoplasmic T-cell enzyme, but do not bear CD26 on their surfaces). These preparations were

incubated with varying concentrations of Val-boroPro, and enzymatic activity was determined

i o by measuring the accumulation of the fluorescent cleavage product of $7\text{-}\mathrm{amino}$

trifluoromethylcoumarin (AFQ released from the substrate Ala-ProAFC upon

enzymatic cleavage. Val-boroPro inhibited both the enzyme DPPIV and the cytoplasmic T-cell enzyme in the Jurkat preparation.

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DETD . . . neoplasms are interesting as targets for treatment, notably leukaemia such as acute leukemia (AL), chronic leukemia (CL), T-cell acute leukemia (T-ALL), B-cell acute leukemia (B-ALL), T-cell chronic leukemia (T-CLL), B-cell chronic leukemia (B-CLL), prolymphocytic leukemia (PLL), acute undifferentiated leukemia (AUL), acute myelogenous leukemia 5 (AML), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), . . . pro-B-ALL; lymphoma such as Burkitt's lymphoma (BL), non-Hodgkins lymphoma (NHL), Hodgkins lymphoma (HL), follicular lymphoma (FL), diffuse large cell lymphome (DLCL), T-cell lymphoma, B-cell lymphoma; and myeolodysplasia.

alpha makroglobulin, tumour associated trypsin inhibitor, urinary trypsin inhibitor, leupeptin, pyrogluta-myl-Leu-Arg-CHO, 6-aminocaproic acid, p-aminobenzamidine, bis(5-amidino benzimidazolyl)methane, alpha-N-acetyl-L-lysine methyl ester, tosyl-lysine chloromethyl ketone, or Boc-D-Phe-ProBoro-Arg-OH, i.e. all well-known inhibitors of the plasminogen/plasmin system which may be used in vivo with acceptable toxicity.

they all rely on the use of a carrier molecule having a high affinity for the chosen tissue (such as a carrier antibody or fragment thereof) to which is covalently or non-covalently linked the active substance in question. For the purposes of the present invention, an antibody (or fragment thereof) directed against a specific antigens overexpressed in tumours (such as carcino-embryonic antigen, Lewis antigen, transferrin, multi-drug resistance pump, glucose. . .

CLMEN. . . alpha makroglobulin, tumour associated trypsin inhibitor, urinary trypsin inhibitor, leupeptin, pyroglutamyl-Leu-Arg-CHO, 6-aminocaproic acid, p-aminobenz-amidine, bis(5-amidino benzimidazolyl)methane, alpha-N-acetyl-L-lysine methyl ester, tosyl-lysine chloromethyl ketone, and Boc-D-Phe-ProBoro-Arg-OH.

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FILE 'PCTFULL' ENTERED AT 08:18:10 ON 29 JUN 2006
L1 39 S BOROPRO OR PROBORO OR VALBOROPRO
L2 24 S ANTIBOD? AND L1
L3 357416 S ADDITIVE OR SYNERG? OR ENHANC?

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L4
             22 S L3 AND L2
L5
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L6
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L7
              0 S L6 AND CD20
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              3 S L6 AND LYMPHOMA
L9
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L10
           1049 S ANTI () CD20
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             2 S L10 AND L4
L12
             28 S BOROPROLINE
L13
              2 S L12 AND L10
          25810 S B () CELL
L14
L15
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L16
              2 S L2 AND CD20
L17
              6 S L15 NOT PY>2001
          98755 S CANCER? OR NEOPLAS? OR TUMOR?
L18
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L19
             5 L18 AND L17
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     FILE 'DGENE' ENTERED AT 08:18:01 ON 29 JUN 2006
     FILE 'PCTFULL' ENTERED AT 08:18:10 ON 29 JUN 2006
T.1
             39 S BOROPRO OR PROBORO OR VALBOROPRO
L2 '
             24 S ANTIBOD? AND L1
L3
         357416 S ADDITIVE OR SYNERG? OR ENHANC?
T.4
             22 S L3 AND L2
L5
             12 S L4 NOT PY>2001
T.6
             10 S L4 NOT PY>2000
L7
             0 S L6 AND CD20
L8
              3 S L6 AND LYMPHOMA
L9
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L10
           1049 S ANTI () CD20
L11
             2 S L10 AND L4
L12
             28 S BOROPROLINE
             2 S L12 AND L10
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          25810 S B () CELL
L14
L15
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L16
              2 S L2 AND CD20
L17
              6 S L15 NOT PY>2001
          98755 S CANCER? OR NEOPLAS? OR TUMOR?
L18
L19
              5 S L18 AND L17
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L19
       ANSWER 1 OF 5
                         PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:
                        2001016301 PCTFULL ED 20020828
                        QUIESCENT CELL DIPEPTIDYL PEPTIDASE: A NOVEL
TITLE (ENGLISH):
                        CYTOPLASMIC SERINE PROTEASE
TITLE (FRENCH):
                        DIPEPTIDYL PEPTIDASE DE CELLULE QUIESCENTE: UNE
                        NOUVELLE SERINE PROTEASE CYTOPLASMIQUE
INVENTOR(S):
                        HUBER, Brigitte, T.;
                        UNDERWOOD, Robert, H.
PATENT ASSIGNEE(S):
                        TUFTS UNIVERSITY;
                        HUBER, Brigitte, T.;
                        UNDERWOOD, Robert, H.
DOCUMENT TYPE:
                        Patent
PATENT INFORMATION:
                        NUMBER
                                           KIND
                                                    DATE
                        WO 2001016301
                                      A1 20010308
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DESIGNATED STATES

₩. AU CA JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE APPLICATION INFO.: WO 2000-US24052 A 20000901 PRIORITY INFO.: US 1999-09/388,413 19990901 L19 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN ACCESSION NUMBER: 1999017799 PCTFULL ED 20020515 TITLE (ENGLISH): CYTOPLASMIC DIPEPTIDYLPEPTIDASE IV FROM HUMAN T-CELLS TITLE (FRENCH): . DIPEPTIDYLPEPTIDASE IV CYTOPLASMIQUE PROVENANT DE LYMPHOCYTES T D'ORIGINE HUMAINE INVENTOR(S): BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.; HUBER, Brigitte, T.; UNDERWOOD, Robert; KABCENELL, Alisa, K.; SNOW, Roger, J. TRUSTEES OF TUFTS COLLEGE ET AL. PATENT ASSIGNEE(S): LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND DATE -----WO 9917799 A1 19990415 DESIGNATED STATES w • AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG APPLICATION INFO.: WO 1998-US20968 A 19981006 PRIORITY INFO.: US 1997-08/944,265 19971006 L19 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN ACCESSION NUMBER: 1999016864 PCTFULL ED 20020515 TITLE (ENGLISH): STIMULATION OF HEMATOPOIETIC CELLS IN VITRO TITLE (FRENCH): STIMULATION DE CELLULES HEMATOPOIETIQUES IN VITRO INVENTOR(S): BACHOVCHIN, William; WALLNER, Barbara PATENT ASSIGNEE(S): POINT THERAPEUTICS, INC. LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent PATENT INFORMATION: NUMBER KIND DATE -----WO 9916864 A1 19990408 DESIGNATED STATES W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US20343 A 19980929 PRIORITY INFO.: US 1997-60/060,306 19970929

L19 ANSWER 4 OF 5
ACCESSION NUMBER:
TITLE (ENGLISH):
TITLE (FRENCH):
INVENTOR(S):

PCTFULL COPYRIGHT 2006 Univentio on STN 1998024474 PCTFULL ED 20020514 INHIBITION OF INVASIVE REMODELLING INHIBITION DU REMODELAGE INVASIF LUND, Leif, Roge;

DANO, Keld; STEPHENS, Ross; BRueNNER, Nils; SOLBERG, Helene; HOLST-HANSEN, Claus;

NIELSEN, John, Romer

PATENT ASSIGNEE(S): FONDEN TIL FREMME AF EKSPERIMENTEL CANCERFORSKNING;

LUND, Leif, Roge; DANO, Keld; STEPHENS, Ross; BRUENNER, Nils; SOLBERG, Helene;

HOLST-HANSEN, Claus; NIELSEN, John, Romer

LANGUAGE OF PUBL.: English DOCUMENT TYPE: Patent

PATENT INFORMATION:

DESIGNATED STATES

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CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1997-DK555 A 19971208 PRIORITY INFO.: DK 1996-1402/96 19961206

L19 ANSWER 5 OF 5

PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1998000439 PCTFULL ED 20020514

TITLE (ENGLISH):

MULTIVALENT COMPOUNDS FOR CROSS-LINKING RECEPTORS AND

USES THEREOF

TITLE (FRENCH):

COMPOSES MULTIVALENTS POUR LA RETICULATION DE

RECEPTEURS ET UTILISATIONS ASSOCIES

INVENTOR(S):

BACHOVCHIN, William, W. TRUSTEES OF TUFTS COLLEGE;

BACHOVCHIN, William, W.

LANGUAGE OF PUBL.:

PATENT ASSIGNEE(S):

DOCUMENT TYPE:

English Patent

PATENT INFORMATION:

NUMBER KIND DATE
----WO 9800439 A2 19980108

DESIGNATED STATES

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NE SN TD TG

APPLICATION INFO.: PRIORITY INFO.:

WO 1997-US11279 A 19970627 US 1996-8/671,756 19960628 US 1997-8/837,305 19970411

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0 WO 0071135/PN (WO71135/PN)

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L21 1 WO 2000071135/PN (WO2000071135/PN)

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ENTRY

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TOTAL

55.91

SESSION

COST IN U.S. DOLLARS

FULL ESTIMATED COST